MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 18, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: Metabolic and Endocrine Advisory Committee for NDA 21-318, Forteo (teriparatide)

SUBJECT: Overview of issues to be discussed at July 27, 2001 Advisory Committee meeting

On July 27, 2001, the Metabolic and Endocrine Advisory Committee will convene to discuss the data on the safety and efficacy of teriparatide for the treatment of osteoporosis in men and post-menopausal women. This memorandum is intended to outline the major issues about which we will be asking for input and comment from the committee.

Teriparatide is recombinant human parathyroid hormone (1-34), identical in sequence to the native N-terminal 34 amino acids of human PTH. Intermittent (daily) subcutaneous injections of teriparatide in animals results in increased bone mass, apparent favorable effects on bone microarchitecture, and increased bone strength by biomechanical testing. Teriparatide clinical safety and efficacy were studied in separate investigational programs in men and postmenopausal women with osteoporosis. Discussed further below, the phase 3 trials were terminated early because of the finding of osteosarcomas in the 2-year rat carcinogenicity study, resulting in a mean of 11 months of exposure among the men and a mean 19 months of exposure among the postmenopausal women.

Teriparatide treatment at two different doses was associated with statistically significant increases in lumbar spine BMD and reductions in the rate of morphometric vertebral fractures in women with post-menopausal osteoporosis and with statistically significant increases in lumbar spine BMD in men with osteoporosis. In both populations, the outcomes for the non-primary endpoints (i.e., BMD and fractures at non-vertebral sites and effect on markers of bone turnover) were, in general, consistent with those of the primary endpoints and thus supportive of its efficacy as a bone anabolic agent when administered daily at the doses studied, 20 and 40 ug. Of note, the major effects of PTH are seen at sites where cancellous bone predominates (i.e., lumbar spine), and the effects are less evident at sites of predominantly cortical bone (i.e., distal radius).

The finding of a dose-related incidence of osteosarcomas in rats treated in a 2-year carcinogenicity study continues to trouble the FDA. Despite the lack of evidence from the medical literature that humans with long-standing primary or secondary hyperparathyroidism are at increased risk for osteosarcoma and the fact that there have been no cases to date in the

relatively small number of people exposed in clinical trials of teriparatide, the risk of this biologically plausible, if theoretical, catastrophic adverse effect in humans treated with daily, bolus PTH is simply not known. You will hear presentations of proposals and plans for post-marketing surveillance for osteosarcomas as well as for a case-control investigational approach to the assessment of causality and risk in the event that cases are identified in patients treated with teriparatide.

The package you have received from FDA contains, in addition to the day's program and a listing of the members of the committee, the review of clinical efficacy, a separate review of clinical safety, the statistician's review of the efficacy data, and the review of the non-clinical pharmacology and toxicology. We have also forwarded draft questions to you under separate cover.

In addition to whatever questions you may raise after reading the briefing documents and hearing the presentations, we would like you to address several issues in your discussion. You will be asked whether there are sufficient data to establish the efficacy of teriparatide at a dose of 20 ug daily (as proposed by the sponsor) for the separate indications in men and in postmenopausal women with osteoporosis.

You will also be asked about the adequacy of the data to define the safety profile of teriparatide for the proposed indications, particularly in light of the limitations in the size and duration of the clinical exposure and the possibility of a risk for osteosarcoma.

As is routine in such meetings, you will be asked for input on the approvability, considering the balance of risk and benefit, of teriparatide for the proposed indications. We have asked that you consider, among other things, issues related to recommendations for duration of use, place in the therapeutic armamentarium (e.g., first- or second-line therapy), and target population (e.g., by baseline risk). You will also be asked to comment on how the osteosarcoma findings in rats should be addressed in labeling, should the drug be approved.

Finally, you'll be asked to comment on risk-management, post-approval surveillance, and the need for additional clinical and/or epidemiological studies should the drug be approved.

As part of the Advisory Committee process, the review divisions of CDER routinely provide briefing packages including copies of relevant reviews and other materials to the members of the Committee (and to the sponsor) in advance of the public meeting and according to a carefully defined timeline. In addition, CDER is committed to providing, as much as is possible, completed or nearly completed review documents, which often will contain statements of preliminary reviewer opinion based on the data submitted as well as recommendations for regulatory action.

Members of the Advisory Committee, the public, as well as representatives of the company should understand that the opinions expressed in the reviews contained in the briefing packet represent opinions of the individual reviewer(s), rendered after review of one or more sections of

the NDA, but without the influence of extensive internal Division or Agency discussion and, obviously, without the benefit, in this case, of the presentations to and deliberations by the Metabolic and Endocrine Advisory Committee. These opinions do not represent final Agency judgment nor do they reflect actual or planned Agency regulatory action on the application. Finally, co-signature by the reviewers' immediate supervisors does not imply complete concurrence with recommendations and opinions but rather signifies that the review document and the body of regulatory work that it represents are satisfactory and that therefore the review is acceptable for inclusion in the file and in the briefing packet for the Advisory Committee.

The purpose of the Advisory Committee meeting is to provide an open public forum for unbiased, scientifically-based presentation and discussion of the relevant safety and efficacy information contained in the sponsor's NDA. The FDA convenes these meetings in order to garner the views and comments of outside, non-conflicted experts in the field. We enter into the meeting prepared by our own review of the NDA and of the sponsor's briefing materials, but without a predetermined decision about a course of regulatory action. We identify areas of interest or concern and make every effort to direct our specific questions to the committee to address those areas. We believe we have done so for the upcoming meeting on Forteo. We look forward to an open discussion of the scientific merits of the clinical investigations of Forteo in men and postmenopausal women with osteoporosis and of the specifics of the data generated from these studies.